

Diphtheria

DIPHThERIA IS AN ACUTE, TOXIN-MEDIATED DISEASE caused by *Corynebacterium diphtheriae*. The name of the disease is derived from the Greek *diphthera*, meaning leather hide. The disease was described in the 5th Century B.C. by Hippocrates, and epidemics were described in the 6th Century A.D. by Aetius. The bacterium was first observed in diphtheritic membranes by Klebs in 1883 and cultivated by Löffler in 1884. Antitoxin was invented in late 19th century, and toxoid was developed in the 1920s.

Corynebacterium diphtheriae

C. diphtheriae is an aerobic gram-positive bacillus. Toxin-production (toxigenicity) occurs only when the bacillus is itself infected (lysogenized) by a specific virus (bacteriophage) carrying the genetic information for the toxin (tox gene). Only toxigenic strains can cause severe disease.

Culture of the organism requires selective media containing tellurite. If isolated, the organism must be distinguished in the laboratory from other *Corynebacterium* species that normally inhabit the nasopharynx and skin (e.g., diphtheroids).

There are three biotypes — gravis, intermedius, and mitis. The most severe disease is associated with the gravis biotype, but any strain may produce toxin. All isolates of *C. diphtheriae* should be tested by the laboratory for toxigenicity.

Pathogenesis

Susceptible persons may acquire toxigenic diphtheria bacilli in the nasopharynx. The organism produces a toxin that inhibits cellular protein synthesis and is responsible for local tissue destruction and membrane formation. The toxin produced at the site of the membrane is absorbed into the bloodstream and then distributed to the tissues of

Diphtheria

- Greek *diphtheria* (leather hide)
- Recognized by Hippocrates in 5th century B.C.
- Epidemics described in 6th century
- *C. diphtheriae* described by Klebs in 1883
- Toxoid developed in 1920s

Corynebacterium diphtheriae

- Aerobic gram-positive bacillus
- Toxin production occurs only when *C. diphtheriae* infected by virus (phage) carrying tox gene
- If isolated, must be distinguished from normal diphtheroid

the body. The toxin is responsible for the major complications of myocarditis and neuritis and can also cause low platelet counts (thrombocytopenia) and protein in the urine (proteinuria).

Clinical disease associated with non-toxin-producing strains is generally milder. While rare severe cases have been reported, these may actually have been caused by toxigenic strains which were not detected due to inadequate culture sampling.

Clinical Features

The incubation period of diphtheria is 2-5 days (range, 1-10 days).

Disease can involve almost any mucous membrane. For clinical purposes, it is convenient to classify diphtheria into a number of manifestations, depending on the site of disease.

Anterior nasal diphtheria

The onset is indistinguishable from that of the common cold and is usually characterized by a mucopurulent nasal discharge (containing both mucus and pus) which may become blood-tinged. A white membrane usually forms on the nasal septum. The disease is usually fairly mild because of apparent poor systemic absorption of toxin in this location, and can be terminated rapidly by antitoxin and antibiotic therapy.

Pharyngeal and tonsillar diphtheria

The most common sites of infection are the tonsils and the pharynx. Infection at these sites is usually associated with substantial systemic absorption of toxin. The onset of pharyngitis is insidious. Early symptoms include malaise, sore throat, anorexia, and low-grade fever. Within 2-3 days, a bluish-white membrane forms and extends, varying in size from covering a small patch on the tonsils to covering most of the soft palate. Often by the time a physician is contacted, the membrane is greyish-green in color, or black if there has been bleeding. There is a minimal amount of mucosal erythema surrounding the membrane. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding. Extensive membrane formation may result in respiratory obstruction.

Diphtheria

Clinical Features

- Incubation period 2-5 days (range, 1-10 days)
- May involve any mucous membrane
- Classified based on site of infection:
 - Anterior nasal
 - Tonsillar and pharyngeal
 - Laryngeal
 - Cutaneous
 - Ocular
 - Genital

Pharyngeal and Tonsillar Diphtheria

- Insidious onset of exudative pharyngitis
- Exudate spreads over 2-3 days and may form adherent membrane
- Membrane adherent to pharynx and may cause respiratory obstruction
- Fever usually not high but patient appears toxic

The patient may recover at this point; or if enough toxin is absorbed, develop severe prostration, striking pallor, rapid pulse, stupor, coma, and may even die within 6 to 10 days. Fever is usually not high, even though the patient may appear quite toxic. Patients with severe disease may develop marked edema of the submandibular areas and the anterior neck along with lymphadenopathy, giving a characteristic “bullneck” appearance.

Laryngeal diphtheria

Laryngeal diphtheria can be either an extension of the pharyngeal form or the only site involved. Symptoms include fever, hoarseness, and a barking cough. The membrane can lead to airway obstruction, coma, and death.

Cutaneous (skin) diphtheria

In the United States, cutaneous diphtheria has been most often associated with homeless persons. Skin infections are quite common in the tropics and are probably responsible for the high levels of natural immunity found in these populations. Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and membrane, but any chronic skin lesion may harbor *C. diphtheriae*, along with other organisms. Generally, the organisms isolated from recent cases in the United States were non-toxigenic. In general, the severity of the skin disease with toxigenic strains appears to be less than in other forms of infection with toxigenic strains. Skin diseases associated with nontoxigenic strains are no longer reported to the National Notifiable Diseases Surveillance System in the United States.

Other sites of involvement include the mucous membranes of the conjunctiva and vulvo-vaginal area, as well as the external auditory canal.

Complications

Most complications of diphtheria, including death, are attributable to effects of the toxin. The severity of the disease and complications are generally related to the extent of local disease. The toxin, when absorbed, affects organs and tissues distant from the site of invasion. The most frequent complications of diphtheria are:

Myocarditis

Abnormal cardiac rhythms can occur early in the course of the illness or weeks later, and can lead to heart failure. If myocarditis occurs early, it is often fatal.

Diphtheria Complications

- Most complications and death attributable to toxin
- Severity of complications generally related to extent of local disease
- Most common complications are myocarditis and neuritis
- Death occurs in 5%-10% for respiratory disease, higher in <5 and >40 years

Neuritis

This complication most often affects motor nerves and usually clears completely. Paralysis of the soft palate is most frequent during the third week of illness. Eye muscles, limbs, and diaphragm paralysis can occur after the fifth week. Secondary pneumonia and respiratory failure may result from diaphragmatic paralysis.

Other complications include otitis media and respiratory insufficiency due to airway obstruction, especially in infants.

Death

The overall case-fatality rate for diphtheria is 5%-10%, with higher death rates (up to 20%) in persons <5 and >40 years of age. The case-fatality rate for diphtheria has changed very little during the last 50 years.

Laboratory Diagnosis

Diagnosis is usually made based on the clinical presentation since it is imperative to begin presumptive therapy quickly.

Culture of the lesion is done to confirm the diagnosis. It is critical to take a swab of the pharyngeal area, especially any discolored areas, ulcerations, and tonsillar crypts. Culture medium containing tellurite is preferred because it provides a selective advantage for the growth of this organism. A blood agar plate is also inoculated for the detection of hemolytic streptococcus. If diphtheria bacilli are isolated, they must be tested for toxin production.

Gram stain and Kenyon stain of material from the membrane itself can be helpful when trying to confirm the clinical diagnosis. The Gram stain may show multiple club-shaped forms which look like Chinese characters. Other *Corynebacterium* species ("diphtheroids") that can normally inhabit the throat may confuse the interpretation of direct stain. However, treatment should be started if clinical diphtheria is suggested, even in the absence of a diagnostic Gram stain.

In the event that prior antibiotic therapy may have impeded a positive culture in a suspect diphtheria case, two sources of evidence may aid in presumptive diagnosis: (1) isolation of the *C. diphtheriae* from culturing of close contacts, and/or (2) a low non-protective diphtheria antibody titer in sera obtained prior to antitoxin administration (<0.1 I.U.) This is done by commercial laboratories and requires several days.

To isolate *C. diphtheriae* from carriers, it is best to inoculate a Löffler's or Pai's slant with the throat swab. After an incubation period of 18-24 hours, growth from the slant is used to inoculate a medium containing tellurite.

Medical Management

Diphtheria antitoxin

Diphtheria antitoxin, produced in horses, was first used in the United States in 1891. It is no longer indicated for prophylaxis of contacts of diphtheria cases, only for the treatment of diphtheria.

Antitoxin will not neutralize toxin that is already fixed to tissues, but will neutralize circulating (unbound) toxin and will prevent progression of disease. The patient must be tested for sensitivity before antitoxin is given. Consultation on the use of diphtheria antitoxin is available at all times through the CDC operator at (404) 639-2889 or 2888. During office hours, 8:00 am - 4:30 pm EST, contact staff at the Child Vaccine Preventable Diseases Branch, National Immunization Program, (404) 639-8255.

Persons with suspected diphtheria should be given antibiotics and antitoxin in adequate dosage and placed in isolation after the provisional clinical diagnosis is made and appropriate cultures are obtained. Respiratory support and airway maintenance should also be administered as needed.

Antibiotics

Treatment with erythromycin orally or by injection (40 mg/kg/day; maximum, 2 gm/day) for 14 days, or procaine penicillin G daily, intramuscularly (300,000 U/day for those weighing 10 kg or less and 600,000 U/day for those weighing more than 10 kg) for 14 days. The disease is usually not contagious 48 hours after antibiotics are instituted. Elimination of the organism should be documented by two consecutive negative cultures after therapy is completed.

Preventive measures

For close contacts, especially household contacts, a diphtheria booster, appropriate for age, should be given. Contacts should also receive antibiotics—benzathine penicillin G (600,000 units for persons less than 6 years old and 1,200,000 units for those 6 years old and older) or a 7- to 10-day course of oral erythromycin,

Diphtheria Antitoxin

- First used in 1891
- Produced in horses
- Used only for treatment of diphtheria
- Neutralizes only unbound toxin

(40 mg/kg/day for children and 1 g/day for adults). For compliance reasons, if surveillance of contacts cannot be maintained, they should receive benzathine penicillin G. Identified carriers in the community should also receive antibiotics. Maintain close surveillance and begin anti-toxin at the first signs of illness.

Contacts of cutaneous diphtheria should be handled as above; however, if the strain is shown to be nontoxigenic, investigation of contacts can be discontinued.

Epidemiology

Occurrence

Diphtheria occurs worldwide, but clinical cases are more prevalent in temperate zones. In the United States during the pretoxoid era, the highest incidence was in the Southeast during the winter. More recently, highest incidence rates have been in states with significant populations of Native Americans. No geographic concentration of cases is currently observed in the United States.

Reservoir

Human carriers are usually asymptomatic. In outbreaks, high percentages of children are found to be transient carriers.

Transmission

Transmission is most often person-to-person spread from the respiratory tract. Rarely, transmission may occur from skin lesions or articles soiled with discharges from lesions of infected persons (fomites).

Temporal pattern

In temperate areas, diphtheria most frequently occurs during winter and spring.

Communicability

Transmission may occur as long as virulent bacilli are present in discharges and lesions. The time is variable, but organisms usually persist 2 weeks or less, and seldom more than 4 weeks, without antibiotics. Chronic carriers may shed organisms for 6 months or more. Effective antibiotic therapy promptly terminates shedding.

Diphtheria Epidemiology

- **Reservoir** Human carriers, usually asymptomatic
- **Transmission** Respiratory
Skin and fomites rarely
- **Temporal pattern** Winter and spring
- **Communicability** Up to several weeks without antibiotics

Secular Trends in the United States

Diphtheria was once a major cause of morbidity and mortality among children. In England and Wales during the 1930s, diphtheria was among the top three causes of death for children <15 years of age.

In the 1920s in the United States, 100,000-200,000 cases of diphtheria (140-150 cases per 100,000 population) and 13,000-15,000 deaths were reported each year. In 1921, a total of 206,000 cases and 15,520 deaths were reported. The number of cases gradually fell to about 19,000 cases in 1945 (15 per 100,000 population). A more rapid decrease began with the widespread use of toxoid in the late 1940s.

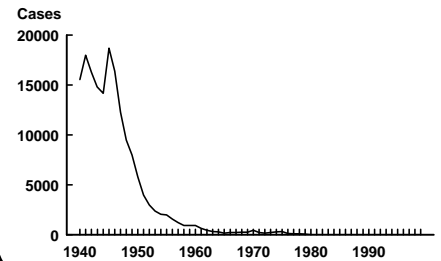
From 1970 to 1979, an average of 196 cases per year were reported. This included a high proportion of cutaneous cases from an outbreak in Washington state. Beginning in 1980, all cases with non-toxigenic cutaneous isolates were excluded from reporting. Diphtheria was seen most frequently in Native Americans and persons in lower socio-economic strata.

From 1980 through 1999, only 49 cases of diphtheria were reported in the United States, an average of 3 per year (range, 0-5 cases per year). No cases were reported in 1993 and 1995. Only one case was reported each year in 1998 and 1999.

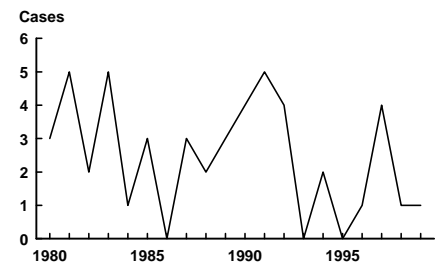
Of 40 reported cases with known age, in 1982-1998, twenty-five (63%) cases were in persons >20 years of age; 38% of cases were among persons >40 years of age. Most cases have occurred in unimmunized or inadequately immunized persons. The current age distribution of cases corroborates the finding of inadequate levels of circulating antitoxin in many adults (up to 60% with less than protective levels).

Although diphtheria disease is rare in the United States, it appears that *Corynebacterium diphtheriae* continues to circulate in areas of the country with previously endemic diphtheria. In 1996, 10 isolates of *C. diphtheriae* were obtained from persons in an American Indian community in South Dakota. Eight of these isolates were toxigenic. None of the infected persons had classic diphtheria disease, although 5 had either pharyngitis or tonsillitis. The presence of toxigenic *C. diphtheriae* in this community is a good reminder for providers not to let down their guard against this organism.

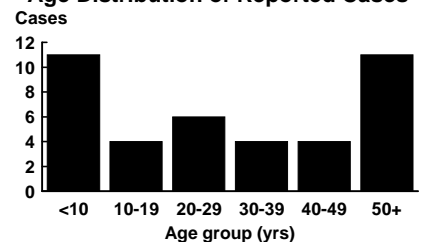
Diphtheria - United States, 1940-1999



Diphtheria - United States, 1980-1999



Diphtheria - United States, 1982-1998
Age Distribution of Reported Cases



Diphtheria in the Newly Independent States

- Outbreak began in 1990 in the Russian Federation
- All 15 NIS affected by 1994
- >50,000 cases and 1,500 deaths in 1995
- Adults account for many cases

Diphtheria continues to occur in other parts of the world. A major epidemic of diphtheria occurred in countries of the former Soviet Union beginning in 1990. By 1994, the epidemic had affected all 15 Newly Independent States (NIS). In 1995 alone, over 50,000 cases and 1,500 deaths from diphtheria were reported. In the six years from 1990 through 1995, the NIS accounted for over 90 percent of all diphtheria cases reported to the World Health Organization from the entire world. In some NIS countries, up to 80% of the epidemic diphtheria cases have been among adults. The outbreak, and the age distribution of cases, is believed to be due to several factors, including a lack of routine immunization of adults in these countries.

Diphtheria Toxoid

Characteristics

Beginning in the early 1900s, prophylaxis was attempted with toxin-antitoxin mixtures. Toxoid was developed around 1921, but was not widely used until the early 1930s. It was incorporated with tetanus toxoid and pertussis vaccine and became routinely used in the 1940s.

Diphtheria toxoid is produced by growing toxigenic *C. diphtheriae* in liquid medium. The filtrate is incubated with formaldehyde to convert toxin to toxoid. It is adsorbed onto an aluminum salt and preserved with thimerosal.

DTaP, DT, and Td

	Diphtheria	Tetanus
DTaP, DT	7-8 Lf units	5-12.5 Lf units

Td (adult)	2 Lf units	5 Lf units
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Pertussis vaccine and pediatric DT used through age 6 years. Adult Td used for persons 7 years and older.

Single antigen diphtheria toxoid is not available. Diphtheria toxoid is available combined with tetanus as pediatric DT or adult Td, and with both tetanus toxoid and acellular pertussis vaccine as DTaP. Combination diphtheria and tetanus toxoids and whole cell pertussis vaccine (DTP) is available but is no longer recommended. Pediatric formulations (DT and DTaP) contain a similar amount of tetanus toxoid as adult Td, but contain 3-4 times as much diphtheria toxoid. Children younger than 7 years of age should receive either DTaP or pediatric DT. Persons 7 years of age or older should receive the adult formulation (adult Td), even if they have not completed a series of DTaP or pediatric DT.

Diphtheria Toxoid

- Formalin-inactivated diphtheria toxin
- Schedule Four doses + booster
Booster every 10 years
- Efficacy Approximately 95%
- Duration Approximately 10 years
- Should be administered with tetanus toxoid as DTaP, DT, or Td

Immunogenicity and vaccine efficacy

After a primary series of three properly spaced diphtheria toxoid doses in adults or four doses in infants, a protective level of antitoxin (defined as >0.1 international units of antitoxin/ml) is reached in over 95%. Diphtheria toxoid has been estimated to have a clinical efficacy of 97%.

Vaccination Schedule and Use

DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine) is the vaccine of choice for children 6 weeks through 6 years of age. The usual schedule is a primary series of 4 doses at 2,4,6, and 15-18 months of age. The first, second, and third doses of DTaP should be separated by a minimum of 4 weeks. The fourth dose should follow the third dose by no less than 6 months.

If a child has a valid contraindication to pertussis vaccine, pediatric DT should be used to complete the vaccination series. If the child is less than 12 months old when the first dose of DT is administered (as DTP, DTaP, or DT), the child should receive a total of four primary DT doses. If the child is 12 months of age or older at the time that the first dose of DT is administered, a third dose 6-12 months after the second completes the primary DT series.

If the fourth dose of DT, DTP or DTaP is administered before the fourth birthday, a booster (fifth) dose is recommended at 4-6 years of age. The fifth dose is not required if the fourth dose was given on or after the fourth birthday.

Because of waning antitoxin titers, most individuals have antitoxin levels below optimal levels 10 years after the last dose. Tetanus toxoid should be given with diphtheria toxoid as Td every 10 years. The first booster dose may be given at 11-12 years of age, if at least 5 years have elapsed since the last dose of DTP, DTaP, or DT. If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

Td is the vaccine of choice for children 7 years old and older, and for adults. A primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6-12 months after the second. A booster dose of Td should be given every 10 years.

Interrupting the recommended schedule or delaying subsequent doses does not reduce the ultimate immunity. There is no need to restart a series regardless of the time elapsed between doses.

Diphtheria disease may not confer immunity. Individuals recovering from diphtheria should begin or complete active immunization with diphtheria toxoid during convalescence. This is less of a concern than with tetanus.

Routine DTaP Primary Vaccination Schedule

Dose	Age	Interval
Primary 1	2 months	---
Primary 2	4 months	4 wks
Primary 3	6 months	4 wks
Primary 4	15-18 months	6 mos

Routine DTaP Schedule Children <7 years of age

Booster Doses

- 4-6 years, before entering school
- 11-12 years of age if >5 years since last dose (Td)
- Every 10 years thereafter (Td)

Routine Td Schedule Persons >7 years of age

Dose	Interval
Primary 1	---
Primary 2	4 wks
Primary 3	6-12 mos
Booster dose every 10 years	

Diphtheria and Tetanus Toxoids Adverse Reactions

- Local reactions (erythema, induration)
- Hypersensitivity reactions (Arthus-type)
- Fever and systemic symptoms uncommon
- Severe systemic reactions rare

Diphtheria and Tetanus Toxoids Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose
- Moderate or severe acute illness

Adverse Reactions Following Vaccination

Local reactions, generally erythema and induration with or without tenderness, are common after the administration of vaccines containing diphtheria antigen. They are usually self-limited and require no therapy. A nodule may be palpable at the injection site for several weeks. Abscess at the site of injection has been reported. Fever and other systemic symptoms are uncommon.

Arthus-type hypersensitivity reactions, characterized by severe local reactions, may occur, particularly in persons who have had multiple prior boosters. These reactions are a result of high circulating levels of diphtheria antitoxin. Arthus reactions do **not** contraindicate subsequent doses of diphtheria toxoid, but the recommended spacing between booster doses should be maintained.

Rarely, severe systemic reactions such as generalized urticaria, anaphylaxis, or neurologic complications have been reported by those receiving diphtheria toxoid.

Contraindications and Precautions to Vaccination

Persons with a history of neurologic or **severe allergic reaction** following a previous dose should not receive additional doses of diphtheria toxoid. Diphtheria toxoid should be deferred for those individuals who have **moderate to severe acute illness**, but persons with mild illness may be vaccinated. Immunosuppression and pregnancy are not contraindications to diphtheria toxoid.

Vaccine Storage and Handling

The vaccine may be shipped without refrigeration if deliverable in 4 days. Refrigerant may be used. It should be refrigerated immediately upon arrival and stored at a temperature of 2°-8°C (35°-46°F). It should **not be frozen** — this reduces potency, and it should not be stored in direct contact with refrigerant.

Suspect Case Investigation and Control

Immediate action on all highly suspect cases (including cutaneous) is warranted until shown not to be toxigenic *C. diphtheriae*. The following action should also be taken for any toxigenic *C. diphtheriae* carriers who are detected.

1. Contact state health department or CDC.
2. Obtain appropriate cultures and preliminary clinical and epidemiological information (including vaccine history).
3. Begin early presumptive treatment with antibiotics and antitoxin. Start antibiotics and antitoxin. Impose strict isolation until at least two cultures are negative 24 hours after antibiotics were stopped.
4. Identify close contacts, especially household members and other persons directly exposed to oral secretions of the patient. Culture all close contacts, regardless of their immunization status. Ideally, culture should be from both throat and nasal swabs. After culture, all contacts should receive antibiotic prophylaxis. Inadequately immunized contacts should receive DTaP/DT/Td boosters. If less than three doses diphtheria toxoid have been given, or vaccination history is unknown, an immediate dose of diphtheria toxoid should be given and the primary series completed according to the current schedule. If >5 years have elapsed since administration of diphtheria toxoid-containing vaccine, a booster dose should be given. If the most recent dose was within 5 years, no booster is required (see the ACIP's 1991 *Diphtheria, Tetanus, and Pertussis: Recommendations for Vaccine Use and Other Preventive Measures* for schedule for children <7 years of age.)

Unimmunized contacts should start a course of DTaP/DT/Td vaccine and be monitored closely for symptoms of diphtheria for 7 days.

5. Treat any confirmed carrier with adequate course of antibiotic, and repeat cultures at a minimum of 2 weeks to assure eradication of the organism. Persons who continue to harbor the organism after treatment with either penicillin or erythromycin should receive an additional 10-day course of erythromycin and should submit samples for follow-up cultures.
6. Treat any contact with antitoxin at the first sign of illness.

Diphtheria Summary

- Toxin mediated
- Fewer than 5 reported cases per year
- Most cases in older persons
- Need for adult immunization

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